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EXAMINER	
DUFFY, BRADLEY	
ART UNIT	**PAPER NUMBER**
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,168	MULLIGAN ET AL.	
	Examiner	Art Unit	
	BRADLEY DUFFY	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18,19,23-26,28,29,31 and 39* is/are pending in the application.

4a) Of the above claim(s) *19,28,29 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18,23-26 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 May 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/17/07, 2/20/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Exhibit A*.

DETAILED ACTION

1. The amendment filed March 7, 2008, is acknowledged and has been entered. Claims 18, 19, 23-26 and 28 have been amended. Claim 27 has been canceled. Claim 39 is newly added.

2. The election with traverse filed March 7, 2008, is acknowledged and has been entered.

Applicant has elected the invention of Group I, Claims 18 and 23-27, directed to a monoclonal antibody obtainable from a hybridoma cell of, or derived from, ECACC Deposit No. 03073001 or fragment thereof; and a diagnostic kit or biological targeting device comprising said antibody or fragment. Newly added claim 39 which is drawn to a hybridoma cell of ECACC Deposit No. 03073001 is part of the invention of Group I.

3. Claims 18, 19, 23-26, 28, 29, 31 and 39 are pending in the application.

4. Claims 19, 28, 29 and 31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed March 7, 2008.

5. Claims 18, 23-26 and 39 are under examination.

Election/Restrictions

6. Applicant's traversal of the restriction and election requirement set forth in the Office action mailed January 8, 2008, is acknowledged.

Applicant's arguments have been carefully considered but have not been found persuasive for the following reasons:

Applicant appears to be traversing the restriction requirement on the grounds that the claims have now been amended to comprise a special technical feature which distinguishes over the prior art. Based on this amendment Applicant requests withdrawal of the restriction requirement and rejoinder of all pending groups

In response, Applicant's request for rejoinder is currently premature because all the claims drawn to the elected invention are not allowable. Notably, as set forth in MPEP 1893.03(d), "If an examiner (1) determines that the claims lack unity of invention and (2) requires election of a single invention, when all of the claims drawn to the elected invention are allowable (i.e., meet the requirements of 35 U.S.C. 101, 102, 103 and 112), the nonelected invention(s) should be considered for rejoinder".

Therefore, because all the claims drawn to the elected invention are not allowable, for the reasons set forth below, Applicant's request for rejoinder is currently moot and the restriction requirement has not been obviated. Furthermore, it is noted that PCT Rules 13.1 and 13.2 do not provide for a single general inventive concept to comprise more than the first mentioned product, the first mentioned method for making said product, and the first mentioned method for using said product.

Therefore, for these reasons and the reasons set forth in the Office action mailed January 8, 2008, the restriction/election requirement is deemed proper and therefore made FINAL.

Information Disclosure Statement

7. The references cited in the information disclosure statement filed on January 17, 2007, have been considered. Notably, the information disclosure statement filed 2/20/2007 merely provided copies of some of the references cited in the information disclosure statement filed on January 17, 2007, which were not provided on January 17, 2007.

Drawings

8. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they do not include the following reference sign(s) mentioned in the description: In this case, Figure 2 is disclosed in the specification at page 9 as containing panels labeled A-G; yet Figure 2 only has panels labeled A, B and C. Additionally, Figure 6 is disclosed in the specification at page 10 as containing reference characters A-F; yet Figure 6 does not appear to contain these reference characters.

Furthermore, the drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the description: In this case, Figure 8 has panels labeled A and B; yet the description of Figure 8 at page 10 does not mention these panels.

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either “Replacement Sheet” or “New Sheet” pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Appropriate correction is required.

Specification

9. The disclosure is objected to for the following reasons:

(a) The specification is objected to because the Brief Description of the Drawings fails to comply with 37 CFR 1.84(p)(5) which requires every reference character to be described in the brief description. In this case, the brief description of the drawings does not specifically refer to panels A and B presented in Figure 8.

(b) The disclosure is objected to because the disclosure refers to embedded hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified. Reference to hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified is impermissible and therefore requires deletion.

Examples of such impermissible disclosures appear in the specification at, for example, paragraph at page 16, lines 26-31 and paragraph at page 17, lines 7-12 as amended March 7, 2008.

The attempt to incorporate essential or non-essential subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP § 608.01(p), paragraph I regarding acceptable incorporation by reference. See 37 CFR § 1.57.

MPEP 608.01(p) does not provide for incorporation of essential *or* non-essential material by reference to, for example, hyperlinks or other forms of browser-executable code. Essential subject matter may only be incorporated by reference to (1) US patents and pending US applications, or patents or other publications published by a foreign country or a regional patent office, (2) non-patent publications, (3) a US patent or application which itself incorporates material by reference, or (4) a foreign application. Non-essential information may be incorporated by reference to (1) patents or applications published by the United States, or patents or other publications published by a foreign country or a regional patent office, (2) prior filed, commonly owned US applications, (3) non-patent publications.

It is impermissible that a patent's disclosure incorporate essential or non-essential material by reference to, for example, embedded hyperlinks and/or other forms of browser-executable code, because the information contained in the websites or databases to which the hyperlinks or other forms of browser-executable code connect may not be maintained on the Internet for the duration of the patent's term and may not contain the same information after the filing date of an application that was contained in the website or database on or before the filing date of the application. Since the information contained in a website may vary, it is not evident that information contained in a website will always remain useful to the practitioner or even applicable to the invention; and information contained in an extinct website cannot possibly be helpful to the practitioner. Furthermore, the validity of a patent containing a reference to a hyperlink or other form of browser-executable code may be reasonably questioned if the website(s) to which the hyperlink(s) connect were relied upon by the patentee(s) to provide sufficient disclosure or description of the invention to meet the requirements of 35 USC § 112, first and second paragraphs. As such, recitation of such references is not permitted.

A hyperlink or other form of browser-executable code may be permitted if the hyperlink or other form of browser-executable code is part of the claimed invention, but in such a case, the Office would disable the hyperlink or other form of browser-executable code.

In general, if the Applicant expects to rely upon the information contained in the websites or databases to provide antecedent basis for the subject matter of claims in a parent application or related applications, and if the material is properly incorporated by reference in the referencing application, Applicant would be required to amend the specification of the referencing application to include the material incorporated by reference to the hyperlink or other forms of browser-executable web, or other non-permissible sources and to provide a declaration by Applicant or Applicant's representative stating that the amendatory material consists of the same material incorporated by reference in this application. See MPEP § 608.01(p).

If Applicant intends that information contained at the websites to which the disclosures refer be incorporated, Applicant is required to amend the specification to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by Applicant, or a practitioner representing Applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

(c) The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Examples of such improperly demarcated trademarks appearing in the specification are Sepharose® (see page 11) and Lipofectin® (see page 24). Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at <http://www.uspto.gov/web/menu/search.html>.

(d) The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 18 and 23-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 18 and 23-26 are indefinite for the recitation of "a monoclonal antibody *obtainable* from a hybridoma cell". What is a monoclonal antibody *obtainable* from a hybridoma cell? Is it an antibody produced by the hybridoma, an antibody cloned from the hybridoma, an antibody produced by immunizing a host with an antigen expressed by the hybridoma, an antibody produced by expressing an antibody expression construct in the hybridoma, and antibody somehow derived from the antibody produced by the hybridoma or is the antibody obtained from the hybridoma cell in some other way? Therefore, it is submitted that the metes and bounds of the subject matter that is regarded as the invention is not delineated with the clarity and particularity to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, so as permit the skilled artisan to know or determine infringing subject matter.

(b) Claims 23-26 are also indefinite for the recitation of "a primary antibody according to Claim 18", because claim 18 only refers to monoclonal antibodies and does not refer to a primary antibody. Accordingly, there is no antecedent basis in claim 18 to support this recitation in claim 23. Because of the ambiguity that results from the lack of antecedent basis supporting the recitation, it is unclear which (if any) "primary antibody according to claim 18" is being referred to in claim 23. For these reasons, the claims fail to delineate the metes and bounds of the subject matter regarded as the invention with the clarity and particularity necessary to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, so as to permit the skilled artisan to know or determine infringing subject matter.

Accordingly, these claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 18 and 23-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description'' Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereinafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This

> problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

Furthermore, the Federal Circuit has commented that each case involving the issue of written description, "must be decided on its own facts. Thus, the precedential value of cases in this area is extremely limited." *Vas-Cath*, 935 F.2d at 1562 (quoting *In re Driscoll*, 562 F.2d 1245, 1250 (C.C.P.A. 1977)). See *Noelle v. Lederman*, 69 USPQ2d 1508 (CAFC 2004).

Finally, with further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention*.

In the instant case, the claims are broadly drawn to a structurally and functionally diverse genus of "monoclonal antibodies *obtainable* from a hybridoma cell of ECACC Deposit No.03073001" or an antigen binding fragment thereof. Claim 26 is

further drawn to an antibody according to claim 18 or an antigen-binding fragment thereof, and a therapeutic ligand comprised in a structurally and functionally diverse genus of "biological targeting devices". However, in this case, the written description only adequately describes the monoclonal antibody *produced* by the hybridoma cell line deposited as ECACC Deposit No. 03073001 and antigen-binding fragments of said monoclonal antibody (see page 4, lines 1-11, page 12, line 28 to page 13, line 29 and page 17, line 16 to page 18, line 1). Furthermore, while the specification adequately describes a composition comprising the monoclonal antibody *produced* by the hybridoma cell line deposited as ECACC Deposit No. 03073001 (see page 13, lines 24-25), as will be explained in further detail below, the specification does not adequately describe the structurally and functionally diverse genus of "biological targeting devices".

To first address the reasons why the specification does not adequately describe the genus of "monoclonal antibodies *obtainable* from a hybridoma cell of ECACC Deposit No.03073001" it is noted that the specification at page 4 discloses that:

> In another aspect, the invention relates to a monoclonal antibody obtainable from a hybridoma cell of, or derived from, ECACC Deposit No. 03073001.

Notably, the specification does not provide any guidance as to which monoclonal antibodies could be obtained or derived from a hybridoma cell of ECACC Deposit No. 03073001, nor does it set forth any particularly identifying structural feature that this genus of monoclonal antibodies would necessarily have. As the monoclonal antibodies need only to be able to be obtained from a hybridoma cell of ECACC Deposit No. 03073001, it is submitted that the genus of "monoclonal antibodies *obtainable* from a hybridoma cell of ECACC Deposit No.03073001" is inclusive of a structurally and functionally diverse genus of antibodies that need not bind any particular antigen and includes any antibodies that could be obtained or derived from a hybridoma cell of ECACC Deposit No. 03073001. Furthermore, the claims do not require the "monoclonal antibodies *obtainable* from a hybridoma cell of ECACC Deposit No.03073001" to have any particular function and therefore there can be no correlation of any particular identifying structural feature with any function of the claimed antibodies. Thus, the

specification fails to adequately describe these antibodies, as a whole, because the skilled artisan could not immediately envision, recognize or distinguish as least most of its members from other antibodies, as the specification fails to describe its members as sharing any particularly identifying (i.e., substantial) structural feature, which correlates with any one particularly identifying functional feature that is also shared by many, if not all, of those antibodies.

In this case, given the lack of particularity with which the genus of "monoclonal antibodies *obtainable* from a hybridoma cell of ECACC Deposit No.03073001" is described, it is submitted that the claims are directed to any monoclonal antibody that could be obtained by e.g., recombinant expression of the antibody in a hybridoma cell. Notably, this position is supported by claim 24 which recites that the antibody comprises a detectable label because, generally speaking, the monoclonal antibody produced by the hybridoma cell line deposited as ECACC Deposit No.03073001 is not detectably labeled. Accordingly, to obtain a monoclonal antibody comprising a detectable label would require further manipulation of the antibody and it is clear that the claims broadly encompass any monoclonal antibodies which might be expressed in such a cell line or are otherwise obtainable from the cell line. By way of further explanation, because methods of recombinant expression of monoclonal antibodies are well-known in the art and because hybridoma cells are capable of expressing functional antibodies (see e.g., Antibody Engineering: A Practical Approach, (Edited by McCafferty et al, Oxford Univeristy Press: pages 282 and 283, 1996) , one of skill in the art could reasonably obtain any monoclonal antibody that has been cloned by recombinant DNA methods by expressing it in a hybridoma cell of ECACC Deposit No.03073001. For example, Shearman et al (J. Immun., 147(12):4366-4373, 1991) teach a humanized monoclonal antibody that has been cloned into mammalian expression vectors and transfected into a murine hybridoma cell line and expressed in that cell line. Shearman et al further teach that this monoclonal antibody has specificity for the human α/β TCR antigen (see entire document, e.g., abstract and page 4367). Therefore, because the humanized monoclonal antibody of Shearman et al can be expressed in murine hybridoma cells,

such as a hybridoma cell of ECACC Deposit No.03073001, this monoclonal antibody is reasonably considered to be *obtainable* from a hybridoma cell of ECACC Deposit No.03073001. Notably, the humanized monoclonal antibody of Sherman et al binds a completely distinct antigen than the monoclonal antibody *produced* by the hybridoma cell line deposited as ECACC Deposit No.03073001, the only particularly described "antibody", which is a member of this broad genus of "monoclonal antibodies *obtainable* from a hybridoma cell of ECACC Deposit No.03073001". Accordingly, because "monoclonal antibodies *obtainable* from a hybridoma cell of ECACC Deposit No.03073001", need not bind any particular antigen, one of skill in the art would not recognize that the monoclonal antibody *produced* by the hybridoma cell line deposited as ECACC Deposit No.03073001 was representative of any other antibodies in this genus which bind to such structurally and functionally diverse antigens. For these reasons, one of skill in the art would not recognize that Applicant was in possession of the structurally and functionally diverse genus of "monoclonal antibodies *obtainable* from a hybridoma cell of ECACC Deposit No.03073001".

Secondly, to address the reasons why the specification does not adequately describe the genus of "biological targeting devices" it is noted that the specification at page 5 discloses that:

> The invention also relates to a biological targeting device comprising an antibody, typically a monoclonal antibody, of the invention, or a fragment thereof, and a therapeutic ligand.

In this case as well, the specification does not provide any guidance that sets forth any particularly identifying structural feature that this genus of biological targeting devices would necessarily have. Furthermore, the claims do not require the "biological targeting device" to have any particular function and therefore there can be no correlation of any particular identifying structural feature with any function of the claimed "biological targeting devices". Thus, the specification fails to adequately describe these devices, as a whole, because the skilled artisan could not immediately envision, recognize or distinguish as least most of its members from other devices, as the specification fails to describe its members as sharing any particularly identifying (i.e.,

substantial) structural feature, which correlates with any one particularly identifying functional feature that is also shared by many, if not all, of those devices.

Given the lack of particularity with which the "biological targeting devices", to which the claim is directed, are described in the specification, it is submitted that the skilled artisan could not immediately envision, recognize or distinguish at least most of the members of the genus of "biological targeting devices""; and therefore the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

14. Claims 18, 23-26 and 38 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

In this case, while claims 18, 23-26 are not solely limited to the monoclonal antibody *produced* by the hybridoma cell line deposited as ECACC Deposit No. 03073001, as explained in the above rejection of the claims as lacking adequate written description, the claims encompass such an antibody. Furthermore, Claim 39 is drawn to a hybridoma of ECACC Deposit No. 03073001.

It is unclear if the hybridoma cell line deposited as ECACC Deposit No. 03073001, which produces an antibody having the exact chemical identity of the antibody MQ1 is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different VH chains (about 50% homologous) can combine with the same VK chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different VH sequences combine with different VK sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementary-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY page 242 (William E. Paul, M.D. ed., 3d ed; 1993]. Therefore, it would require undue experimentation to reproduce the hybridoma cell line deposited as ECACC Deposit No. 03073001.

While a statement of biological deposit was filed 12/7/2006 for the hybridoma cell line deposited as ECACC Deposit No. 03073001 by an attorney of record, this statement is insufficient to provide the needed assurances that all the conditions of 37 CFR 1.801-1.809 have been met. Notably, while the statement establishes that the deposit was made under the provisions of the Budapest Treaty and that all restrictions imposed on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, the statement does not establish that the deposit will be replaced if viable samples cannot be dispensed by the depository and that access to the deposit will be available during pendency of the patent application making reference to the deposit to one determined by the Commissioner to be entitled thereto under 37 CFR 1.14 and 35 U.S.C. 122. Accordingly, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the hybridoma cell line deposited as ECACC Deposit No. 03073001 will be replaced if viable samples cannot be dispensed by the depository and that access to the deposit will be available during pendency of the patent application making reference to the deposit to one determined by the Commissioner to be entitled thereto under 37 CFR 1.14 and 35 U.S.C. 122 is required. This requirement

is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves these specific matters to the discretion of each State.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

15. As noted above, the claims are not solely limited to the monoclonal antibody *produced* by the hybridoma cell line deposited as ECACC Deposit No. 03073001. As will be explained in more detail below, Claims 18 and 23-26 are also rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and using** any antibodies encompassed by the claims, which have been described by the prior art, **does not reasonably provide enablement for making and using** the claimed monoclonal antibodies *obtainable* from a hybridoma cell of ECACC Deposit No.03073001, diagnostic kits for diagnosing the presence of a cell selected from the group consisting of astrocytoma cells, malignant melanoma secondary tumor cells and primary breast carcinoma cells or biological targeting devices. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue experimentation.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

As set forth in the above rejection of the claims as lacking adequate written description, "monoclonal antibodies *obtainable* from a hybridoma cell of ECACC Deposit No.03073001" are inclusive of antibodies that need not bind any particular antigen and include any antibodies that could be *obtained* or *derived* from a hybridoma cell of ECACC Deposit No. 03073001. Accordingly, it is submitted that one of skill in the art would be subject to undue and unreasonable experimentation to make and use antibodies commensurate in scope with the claimed invention, because the specification does not provide any specific, non-general guidance as to which antibodies could be obtained or derived from a hybridoma cell of ECACC Deposit No. 03073001.

In this case, it is well-established in the art the structural basis of antigen-antibody recognition is characterized by a high level of unpredictability, since the skilled artisan also still cannot accurately and reliably predict the consequences of amino acid substitutions, insertions, and deletions in the antigen-binding domains and surrounding framework regions of antibodies. For example, Giusti et al. (*Proc. Natl. Acad. Sci. USA.* 1987 May; 84 (9): 2926-2930) teaches the specificity and affinity of an antibody is exquisitely sensitive to amino acid substitutions within the primary structure of the antibody, since only a single amino acid substitution in the heavy chain of an antibody completely altered the binding specificity of an antibody that binds phosphocholine,

such that the altered antibody fails to bind phosphocholine but instead binds DNA; see entire document (e.g., the abstract). Chien et al. (*Proc. Natl. Acad. Sci. USA.* 1989 Jul; 86 (14): 5532-5536) teaches that significant structural and functional changes in an antigen-binding site can be caused by amino acid substitutions in the primary structure of an antibody, including substitutions at a site remote from the complementarity determining regions of the antigen-binding domain; see entire document (e.g., the abstract). Similarly, but more recently, Caldas et al. (*Mol. Immunol.* 2003 May; 39 (15): 941-952) teaches an unexpected effect of substituting a framework residue upon binding specificity during the humanization of an antibody that binds CD18; see entire document (e.g., the abstract). Accordingly, one of skill in the art would be subject to undue experimentation to obtain or derive an antibody from a hybridoma cell of ECACC Deposit No. 03073001 which binds any antigen other than the antigen bound by the monoclonal antibody produced by the hybridoma cell of ECACC Deposit No. 03073001, because one of ordinary skill in the art would not be able to identify the changes that would need to be made in the structure of the antibody to change its specificity from one antigen to another. Similarly, one of skill in the art would be subject to undue experimentation to obtain or derive an antibody which differed in amino acid sequence in the complementarity determining regions of the antigen-binding domain when compared the antibody produced by the hybridoma cell line of ECACC Deposit No. 03073001 because of the unpredictability present in determining which amino acid changes in these regions will affect antibody binding.

Accordingly, while one of skill in the art would be enabled to make and use the monoclonal antibody *produced* by the hybridoma cell line deposited as ECACC Deposit No. 03073001, *once* the deposit requirements are met, one of skill in the art would not reasonably be enabled to make and use a monoclonal antibody *obtainable* from a hybridoma cell ECACC Deposit No. 03073001 even after the deposit requirements are met.

Secondly, to address the reason that Applicant has not enabled one of ordinary skill in the to make and use the claimed “biological targeting devices”, it is noted that the

specification does not provide any specific non-general guidance that sets forth any particularly identifying structural and/or functional features that this genus of biological targeting devices would necessarily have. For this reason, one of skill in the art would be subject to undue experimentation to make and use the claimed “biological targeting devices” which could comprise any structural and/or functional features because they would have to unduly and unreasonably experiment to determine which “biological targeting devices” could be made and then subject to further undue experimentation to determine a use for these “devices".

Applicant is reminded that reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. “Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.” *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

Finally, wherein the claims are drawn to the diagnostic kits comprising a primary antibody according to claim 18 with the intended use for diagnosing the presence of a cell selected from astrocytoma cells, malignant melanoma secondary tumor cells and primary breast carcinoma cells, it is submitted that one of skill in the art would be subject to undue and or unreasonable experimentation to use a diagnostic kit comprising a primary antibody according to claim 18 to diagnose the presence of an astrocytoma cell, a malignant melanoma secondary tumor cell or a primary breast carcinoma cell because the antigen recognized by the monoclonal antibody *produced* by the hybridoma cell line deposited as ECACC Deposit No. 03073001 is expressed on multiple different cell types and therefore, while the monoclonal antibody *produced* by the hybridoma cell line deposited as ECACC Deposit No. 03073001 an antibody might

bind to some astrocytoma cells, malignant melanoma secondary tumor cells and primary breast carcinoma cells it would not be sufficient to differentiate between these cells or any other cell expressing the antigen recognize by this antibody. For this reason one of skill in the art would be subject to undue experimentation to use the claimed diagnostic kit for its stated intended use of diagnosing the presence of a cell selected from astrocytoma cells, malignant melanoma secondary tumor cells and primary breast carcinoma cells.

For example, in this case, the specification teaches that the antigen recognized by the monoclonal antibody *produced* by the hybridoma cell line deposited as ECACC Deposit No. 03073001 is expressed on cell types including human fetal astrocytes, some but not all astrocytomas, some but not all primary breast carcinoma cells, secondary metastatic breast carcinoma cells in the brain and secondary metastatic melanoma cells in the brain (See e.g., pages 18, 20, 22 and 23). However, since some astrocytoma cells and some primary breast carcinoma cells do not express the antigen recognized by the monoclonal antibody *produced* by the hybridoma cell line deposited as ECACC Deposit No. 03073001 one of skill in the art would be subject to undue experimentation to e.g., diagnose the presence of astrocytoma cells or primary breast carcinoma cells which do not express this antigen.

Furthermore, the specification teaches that screening of a cDNA expression library with the MQ1 antibody *produced* by the hybridoma cell line deposited as ECACC Deposit No. 03073001 identified two cDNA clones which express a polypeptide recognized by the MQ1 antibody. Notably, as evidenced by the attached Exhibit A the cDNA clone comprising SEQ ID NO:1 expresses a polypeptide with 100% sequence identity to C-terminal residues 866-1218 of human Jagged1. In this case, Li et al (Nature Gen., 16:243-251, 1997, IDS filed 1/17/2007) teach that human Jagged1 is expressed in various adult human tissues, including stomach, thyroid gland, spinal cord, lymph node, trachea, adrenal gland and bone marrow (see entire document, e.g., page 244). Accordingly, the MQ1 antibody *produced* by the hybridoma cell line deposited as ECACC Deposit No. 03073001 would bind to multiple other cell types which normally

express the human Jagged1 polypeptide and one of skill in the art could not distinguish whether a cell was an astrocytoma cell, a malignant melanoma secondary tumor cell or a primary breast carcinoma cell using the claimed diagnostic kit because the antigen recognized by the monoclonal antibody *produced* by the hybridoma cell line deposited as ECACC Deposit No. 03073001 is expressed in multiple different cell types.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 18, 23, 24 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Shearman et al (J. Immun., 147(12):4366-4373, 1991).

The claims are herein drawn to any monoclonal antibody that could be obtained from a hybridoma cell of ECACC deposit No. 03073001, such as any antibody which has been cloned by recombinant DNA methods. Notably, this position is supported by claim 24 which recites that the antibody comprises a detectable label because, generally speaking, the monoclonal antibody produced by the hybridoma cell line deposited as ECACC Deposit No.03073001 is not detectably labeled. Accordingly, to obtain a monoclonal antibody comprising a label would require further manipulation of

the antibody to comprise such a label, absent a showing otherwise. Therefore, it is submitted that the claims broadly, but reasonably encompass any monoclonal antibodies which could be expressed in a hybridoma cell of ECACC deposit No. 03073001. However, these monoclonal antibodies do not actually have to be expressed in a hybridoma cell of ECACC deposit No. 03073001. Once again, because methods of recombinant expression of monoclonal antibodies are well-known in the art and because hybridoma cells are capable of expressing functional antibodies (see e.g., Antibody Engineering: A Practical Approach, (supra)) it is submitted that any monoclonal antibody that has been cloned by recombinant DNA technologies would be consider to be obtainable from a hybridoma cell of ECACC Deposit No.03073001. Furthermore, while claims 23 and 24 recite a diagnostic kit for diagnosing the presence of a cell selected from the group consisting of: astrocytoma cells, malignant melanoma secondary tumor cells and primary breast carcinoma cells, this recitation is interpreted as an intended use of a composition comprising an antibody according to claim 18. In this case, the specification does not expressly define the phrase “diagnostic kit for diagnosing the presence of a cell” and therefore, it is submitted that this recitation does not materially and/or structurally distinguish a composition comprising such an antibody from a “kit” comprising such an antibody. Similarly, while claim 24 recites that the antibody comprise a “detectable" label, the recitation of "detectable" is merely interpreted as an intended use because this recitation does not materially and/or structurally define the label. Accordingly, the antibody is broadly, but reasonably interpreted to comprise virtually any other component. Finally, while claim 26 recites a “biological targeting device" and a “therapeutic” ligand because the specification does not materially and/or structurally define “biological targeting devices” or a “therapeutic” ligand, these phrases are also being interpreted as a recitation of an intended use. Accordingly, claim 26 is broadly, but reasonably drawn interpreted to be drawn to any composition comprising an antibody a obtainable from a hybridoma cell of ECACC deposit No. 03073001 and a ligand.

Shearman et al (J. Immun., 147(12):4366-4373, 1991) teach a humanized monoclonal antibody that has been cloned into mammalian expression vectors and transfected into a murine hybridoma cell line and expressed in that cell line. Shearman et al further teach that this monoclonal antibody has specificity for the human α/β TCR antigen (see entire document, e.g., abstract and page 4367). Shearman et al further teach said antibody in compositions and, in particular, compositions wherein said antibody comprises FITC. In this case, absent a showing otherwise, the composition comprising a monoclonal antibody comprising FITC, is materially and structurally indistinguishable from the composition comprising an antibody comprising a label recited in claim 24 or the composition comprising an antibody and a ligand recited in claim 26.

In summary, the monoclonal antibody and compositions comprising said monoclonal antibody of the prior art are materially and structurally indistinguishable from the instantly claimed monoclonal antibody and compositions. Therefore, absent a showing of any difference, the claimed monoclonal antibody and compositions and the monoclonal antibody and compositions disclosed by the prior art are deemed the same and Shearman et al anticipates the claimed invention.

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

19. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

20. Claims 23 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shearman et al (J. Immun., 147(12):4366-4373, 1991) in view of Monia et al (US Patent 6,020,199, February 1,2000).

The claims are herein drawn to a composition comprising an antibody according to claim 18 and a secondary antibody which specifically binds said antibody wherein the secondary antibody comprises a label. Once again, as set forth in the above rejection of the claims under 102(b), the phrase "diagnostic kit" and "detectable label" are being interpreted as a recitation of an intended use because these recitations do not materially and/or structurally define the claimed product.

Shearman et al teach what is set forth in the above rejection of the claims under 102(b). Shearman et al do not expressly teach a secondary antibody which specifically binds to their disclosed monoclonal antibody. This deficiency is made up for in the teachings of Monia et al.

Monia et al teach that labeled secondary antibodies are commonly used in immunoassay techniques to specifically bind to an antibody specific for an antigen of interest. (see entire document, e.g., columns 37 and 44).

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to make a composition comprising an antibody specific for human α/β TCR antigen as taught by Shearman et al and at least one labeled secondary antibody that binds this antibody to monitor binding of the Shearman et al antibody to the human α/β TCR antigen by any immunoassay technique.

Notably, one of skill in the art would immediately recognize that labeled secondary antibodies as taught by Monia et al can predictably visualize binding of an antibody specific for human α/β TCR antigen as taught by Shearman et al to the human α/β TCR antigen. Accordingly, one of skill in the art would not have considered it inventive to combine a labeled secondary antibody which predictably visualizes the antibody specific for human α/β TCR antigen with a composition comprising an antibody specific for human α/β TCR antigen as taught by Shearman et al. Furthermore, because labeled secondary antibodies are commonly used along with an antibody specific for an antigen of interest in immunoassays, one of skill in the art would also have reasonably expected that labeled secondary antibodies could be included in compositions comprising an antibody specific for human α/β TCR antigen, in view of these references.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

21. No claims are allowed.

22. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Liao et al (Antican. Res., 21:1673-1680, 2001) teach the DNA

cloning of an scFv monoclonal antibody linked to IL-2 and expressing this monoclonal antibody in hybridoma cells.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Friday 7:00 AM to 4:30 PM, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

/Stephen L. Rawlings/
Primary Examiner, Art Unit 1643

/bd/
Examiner, Art Unit 1643
June 5, 2008